2. GHDH Synopsis

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Clinical Study Report Synopsis: Study B3D-EW-GHDH

Title of Study: Comparison of the effects of Teriparatide with those of Risedronate on lumbar spine volumetric bone mineral density in glucocorticoid-induced osteoporosis in men

Number of Investigators: This multicenter study included 16 principal investigators.

Study Centers: This study was conducted at 16 study centers in 4 countries.

Publication Based on the Study: None at this time.

Length of Study:	**Phase of Development:** III
Date of first patient enrolled: 16 July 2007 Date of last patient completed entire study: 06 October 2010	

Objectives:

Primary objective

The primary objective was to test the hypothesis that teriparatide 20 µg subcutaneously once daily is superior to risedronate 35 mg orally once weekly in the change from baseline to 18 months of lumbar spine volumetric trabecular bone mineral density (BMD) in males with glucocorticoid-induced osteoporosis (GIOP). All patients received elemental calcium 1000 mg orally once daily and vitamin D 800-1200 IU orally once daily.

Secondary objectives

- To test the hypothesis that teriparatide is superior to risedronate in the improvement of the following:
  - Lumbar spine volumetric trabecular BMD, as measured by QCT, at 6 months of treatment.
  - Lumbar spine volumetric integral BMD, as measured by high-resolution QCT (HR-QCT), at 6 and 18 months of treatment.
  - 3-dimensional microstructural variables, as measured by HR-QCT in the 12th thoracic vertebra (T-12), at 6 and 18 months of treatment.
  - Biomechanical variables evaluated by a finite element analysis in T-12, at 6 and 18 months of treatment.
- To compare the effects of teriparatide with those of risedronate, on areal BMD response at the lumbar spine, femoral neck, and total hip, at 18 months of treatment.
- To compare the effects of teriparatide with those of risedronate, on biochemical markers of bone turnover including serum aminoterminal propeptide of type I procollagen (P1NP) and serum type 1 collagen degradation fragments (β-CTx), at 3, 6, and 18 months of treatment.
- To evaluate safety.

An additional exploratory objective of this study was to examine the relationship between biochemical markers of bone turnover and the HR-QCT variables, including finite element analysis, at 6 and 18 months of therapy with teriparatide or risedronate.

Study Design: This study was a Phase 3, multinational, multicenter, randomized, open-label, active comparator controlled study with 2 study periods: a screening phase of up to 6 weeks, and an open-label treatment phase of 18 months. After entry criteria had been fulfilled, patients were randomized in a 1:1 ratio to receive either teriparatide 20 µg/day as a subcutaneous injection or risedronate 35 mg once weekly orally as tablet. The randomization was stratified to assure balance of previous use of bisphosphonates in the 2 treatment groups. After randomization, patients were to receive the study medication for 18 months, with clinical visits after 3, 6, 12, and 18 months.

Number of Patients:

Planned: 100 (50 in each treatment arm)

Randomized: 92 (45 teriparatide, 47 risedronate)

Treated (at least 1 dose): 92 (45 teriparatide, 47 risedronate)

Completed: 77 (38 teriparatide, 39 risedronate)

Diagnosis and Main Criteria for Inclusion: Patients had to be ambulatory men at least 25 years of age with a BMD of at least 1.5 standard deviations below the corresponding normal young adult men average BMD (T score of –1.5 or lower), who had received glucocorticoid therapy at an average dose of at least 5.0 mg/day of prednisone or its equivalent for a minimum of 3 consecutive months immediately preceding screening (Visit 1), and presented with a minimum of 2 lumbar vertebrae in the 1st lumbar vertebra (L-1) through the 3rd lumbar vertebra (L-3) region evaluable by quantitative computerized tomography (QCT).
Patients were excluded if they had a mild, moderate or severe spinal fracture in both T-12 and L-1, abnormal albumin-corrected serum calcium levels as determined by the investigators' site laboratory, or a history of unresolved skeletal diseases that affect bone metabolism other than GIOP.

Test Product, Dose, and Mode of Administration:
Teriparatide 20 μg/day, given once daily as subcutaneous injection.

Comparator, Dose, and Mode of Administration:
Risedronate 5 mg/day (35 mg/week), given once weekly as oral tablet.

Duration of Treatment:
18 months for both treatment groups.

Variables:

Efficacy:

Primary efficacy variable: Change from baseline to 18 months in actual lumbar spine volumetric trabecular BMD as determined by QCT.

Secondary efficacy variables:

- Lumbar spine volumetric trabecular BMD at 6 months as determined by QCT.
- HR-QCT assessments of volumetric integral BMD of T-12, volumetric trabecular BMD of T-12 (or L-1), and of 1 vertebra (T-12 or L-1).
- Finite element analysis: apparent stiffness and bone strength at T-12.
- Areal BMD at the lumbar spine, femoral neck, and total hip by X-ray absorptiometry (DXA).
- Biochemical markers of bone turnover: serum P1NP and serum β-CTx.

Safety:

- Pre-existing conditions and adverse event (AE) reporting.
- Vital signs (diastolic and systolic blood pressure, heart rate) and anthropometry (physical examination, body weight, height, and body mass index [BMI]).
- New clinical fractures.
- Hypercalcemia.

Evaluation Methods:

Efficacy:

Efficacy analyses were based on the Full Analysis Set (FAS), which included all randomized patients who received at least 1 dose of study medication; patients were analyzed as randomized. To be included in the primary efficacy analysis, patients also had to have a lumbar spine volumetric trabecular BMD measurement at baseline and at at least 1 post-baseline visit (primary efficacy population).

Primary Efficacy Analysis

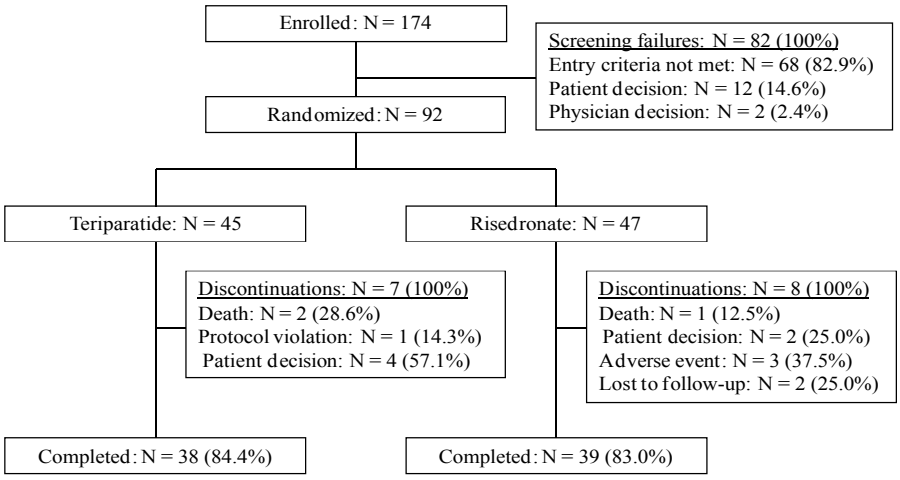
In the primary efficacy analysis a mixed-model repeated measures (MMRM) model was applied on the change from baseline in lumbar spine volumetric trabecular BMD and was fitted using restricted maximum likelihood methods. The model included fixed effects for treatment, visit, and the interaction between treatment and visit, and random effects for patient nested within treatment. Patients were assumed to be independent. In addition, the following variables were included: baseline lumbar spine volumetric trabecular BMD, age, baseline P1NP, whether or not the patient experienced a fracture <12 months prior to study entry, duration of bisphophonate use, baseline glucocorticoid dose and cumulative glucocorticoid dose prior to the trial and during the trial. This model is hereafter referred to as full model.

The unstructured covariance structure for observations within patient across the visits was used. The primary comparison between treatments at 18 months was assessed at the 5% (2-sided) significance level. Degrees of

freedom were estimated using the Kenwood and Roger method.
As a supportive analysis, an MMRM model with fixed effects for treatment, visit, and the interaction between treatment and visit, and random effects for patient nested within treatment was also applied (hereafter referred to as reduced model).
Secondary Efficacy Analyses
The same methods as for the primary comparison at 18 months were applied to the secondary comparison between treatments at 6 months.
Observed volumetric BMD (vBMD) values and changes from baseline were summarized at each visit and compared between treatments at study end using a 2-sample t-test with last observation carried forward (LOCF) applied to those patients without a vBMD assessment at 18 months.
Areal BMD measured by DXA was also analyzed following the methods outlined for vBMD.
Microstructural parameters (from HR-QCT) and biomechanical parameters (finite element analysis) were summarized using descriptive statistics and compared between treatments using an MMRM analysis.
Changes from baseline in bone turn-over markers within and between treatments were assessed using the same mixed models approach as outlined for vBMD.
The Spearman correlation coefficient and its associated p-value were derived at all applicable visits to assess the correlation between bone markers and HR-QCT variables including finite element analysis parameters.
Safety:
Safety analyses were performed on all patients who receive study treatment (safety analysis set); patients were analyzed according to the treatment they received. All safety data, including concomitant medications, AEs, vital signs, and laboratory measurements, were descriptively summarized and treatments were compared using Fisher's exact test, as applicable.

Summary:

Of the 174 patients who were enrolled into the study, 92 were eligible for the study and were randomly assigned to the treatment arms. Forty-five patients received at least 1 dose of teriparatide and 47 at least 1 dose of risedronate. Seven patients in the teriparatide arm compared to 8 patients in the risedronate arm discontinued the study. Patient disposition including the reasons for discontinuation is summarized in Figure GHDH.1.



N = total number of patients.

Figure GHDH.1. Patient disposition

Patient demographics and baseline characteristics are summarized in Table GHDH.1 and showed no major differences between the 2 treatment arms.

Table GHDH.1. Patient Demographics at Baseline Descriptive Statistics (Full Analysis Set)

Variable	Teriparatide (N=45)	Risedronate (N=47)	Total (N=92)
Age (years)			
n	45	47	92
Mean (SD)	57.5 (12.80)	55.1 (15.54)	56.3 (14.24)
Median (range)	58.0 (26.0, 81.0)	56.0 (25.0, 82.0)	57.5 (25.0, 82.0)
Race (n [%])			
Caucasian	44 (97.8)	46 (97.9)	90 (97.8)
Hispanic	0	1 (2.1)	1 (1.1)
East Asian	1 (2.2)	0	1 (1.1)
Number of patients with fractures prior to study (n [%])	19 (42.2)	17 (36.2)	36 (39.1)
Number of fractures per patient			
n	19	17	36
Mean (SD)	1.8 (0.96)	2.0 (1.22)	1.9 (1.08)
Median (range)	2.0 (1.0, 4.0)	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)
Time since last fracture (months)			
n	16	13	29
Mean (SD)	96.9 (143.76)	110.7 (178.24)	103.1 (157.27)
Median (range)	27.8 (2.0, 525.1)	44.9 (4.0, 622.8)	31.5 (2.0, 622.8)

N = Total number of patients; n = Number of available patients; SD = Standard deviation.
Note: All patients were male.

Overall, 31 patients (33.7%) had a previous osteoporosis therapy, 14 patients (31.1%) in the teriparatide arm and 17 patients (36.2%) in the risedronate arm, and almost all of these patients took bisphosphonates.

As required per protocol, all patients were on glucocorticoid therapy prior to the study, mainly for musculoskeletal and connective tissue disorders, respiratory, thoracic and mediastinal disorders, or for gastrointestinal disorders. The median (interquartile range) baseline glucocorticoid dose was 8.8 mg/day (5.0-15.0 mg/day) in the teriparatide arm and 8.8 mg/day (5.0-12.5 mg/day) in the risedronate arm. The median (interquartile range) glucocorticoid therapy duration prior to baseline was 7.1 years (2.3-13.2 years) in the teriparatide arm and 4.9 years (2.5-12.9 years) in the risedronate arm.

Efficacy results

In the teriparatide arm, mean lumbar spine volumetric trabecular BMD increased from 75.7 mg/cm^3 at baseline to 89.4 mg/cm^3 at Month 18, while in the risedronate arm it increased from 78.2 to 86.4 mg/cm^3, respectively. The endpoint analysis results, after applying LOCF, were similar to those seen at Month 18.

The primary objective to show that teriparatide 20 µg subcutaneously once daily is superior to risedronate 35 mg orally once weekly in the change from baseline to 18 months in lumbar spine volumetric trabecular BMD was reached with a statistically significant difference between treatments in favor of teriparatide of 9.34 mg/cm^3 (95% confidence interval: 3.10; 15.59 mg/cm^3; p=0.004), as shown in Table GHDH.2. Results from the reduced model were consistent with those seen in the primary analysis model.

Table GHDH.2. Change from Baseline in Lumbar Spine Volumetric Trabecular Bone Mineral Density (mg/cm^3) Mixed Model Repeated Measures Analysis (Primary Efficacy Population)

	Teriparatide (N=39)		Risedronate (N=40)		Difference (teriparatide – risedronate)		
Time point	LS mean change	SE	LS mean change	SE	Estimate	95% CI	p-value
Primary analysis [a]							
Visit 4/Month 6	4.31	3.15	2.52	3.16	1.79	[-4.37; 7.95]	0.563
Visit 6/Month 18	12.28	3.16	2.94	3.14	9.34	[3.10; 15.59]	0.004
Supportive analysis [b]							
Visit 4/Month 6	5.21	2.12	4.40	2.11	0.81	[-5.18; 6.79]	0.789
Visit 6/Month 18	13.74	2.11	4.82	2.17	8.91	[2.87; 14.96]	0.004

CI = confidence interval; LS = least squares; N = total number of patients; SE = standard error.

[a] Model with fixed effects for treatment, visit, and the interaction between treatment and visit, and random effects for patient nested within treatment, plus the following covariates: age, baseline propeptide of type I procollagen (P1NP), fracture <12 months before study start, duration of prior bisphosphonate use, glucocorticoid doses at screening, before, and after baseline; N=76.

[b] Model with fixed effects for treatment, visit, and the interaction between treatment and visit, and random effects for patient nested within treatment; N=77.

No statistically significant difference was seen between treatments for the change in lumbar spine volumetric trabecular BMD from baseline to Month 6 (Table GHDH.2).

Within-group changes from baseline to endpoint (LOCF) in parameters from the HR-QCT of T-12 were statistically significant across all parameters (including integral BMD) in the teriparatide arm and all parameters but the "cross-sectional area of total vertebral, central slice" in the risedronate arm. However, no statistically significant differences between treatment arms were seen in the MMRM analysis at Month 6 or 18 in any HR-QCT variable, neither with the full model nor with the reduced model.

At Month 18, statistically significant increases in vertebral stiffness and strength were observed within each treatment arm, with statistically significantly higher increases in the teriparatide arm for all tests based in the full MMRM analysis (p-values ≤0.015). Between-treatment differences were not statistically significant at Month 6. Between-treatment comparison results from the reduced MMRM model were comparable with those from the full MMRM model.

Mean changes in areal BMD at the lumbar spine and at the femoral neck were statistically significantly higher with teriparatide than with risedronate after 18 months of treatment: mean

change from baseline in lumbar spine BMD: 0.068 g/cm^2 teriparatide versus 0.037 g/cm^2 risedronate (p=0.045); femoral neck BMD: 0.014 g/cm^2 teriparatide versus -0.007 g/cm^2 risedronate (p=0.026). Changes in total hip BMD were not statistically significantly different between the 2 treatment groups (0.014 versus 0.007 g/cm^2, respectively; p=0.256).

The biochemical markers of bone turnover (P1NP and β-CTx) showed increases from baseline in the teriparatide arm and slight decreases in the risedronate arm at all time points. In the MMRM analysis, differences between treatments in the change from baseline were statistically significant at all time points (p<0.001 [full model]) with the exception of β-CTx at Month 18 (p=0.105). Between-treatment test results from the reduced model were similar to those from the full model.

In the overall population of both treatment arms combined, correlations between bone markers and HR-QCT variables were generally not statistically significant with the exception of very few scattered statistically significant correlation coefficients. Correlation between bone markers and finite element analysis parameters were consistently statistically significant for bone markers at 6 and 18 months and finite element analysis parameters at 18 months (respective correlation coefficients were >0.26).

Safety results

A total of 60 patients (65.2%) experienced 239 treatment-emergent AEs (TEAEs), 25 patients (55.6%) with 107 TEAEs in the teriparatide arm and 35 patients (74.5%) with 132 TEAEs in the risedronate arm (p=0.080). Most commonly reported TEAEs (>5% of patients) were arthralgia (7.6% of patients overall), influenza (7.6%), chronic obstructive pulmonary disease (6.5%), and peripheral edema (5.4%). There were no statistically significant differences between treatment arms in the incidence of TEAEs by system organ class.

A total of 35 patients (38.0%) experienced 58 serious AEs (SAEs), 13 patients (28.9%) with 16 SAEs in the teriparatide arm and 22 patients (46.8%) with 42 SAEs in the risedronate arm (p=0.089). Most commonly reported SAEs (>3% of patients) were chronic obstructive pulmonary disease (5.43% overall) and intervertebral disc protrusion (3.26%).

Three patients died during the study due to an AE: 2 in the teriparatide arm (preferred terms: acute respiratory failure, sudden death) and 1 in the risedronate arm (chronic obstructive pulmonary disease). An additional 3 patients, all in the risedronate arm, discontinued the study due to a TEAE (1 serious case each of intestinal adenocarcinoma, seminoma, and cognitive disorder). These events leading to death or discontinuation were not considered by the investigator to be related to study medication or any study procedure.

None of the patients in the teriparatide arm compared to 5 patients in the risedronate arm (10.6%) had a new clinical fracture during the study (p=0.056). The 5 patients in the risedronate arm had a total of 11 non-vertebral fractures. No clinical vertebral fractures were reported during the study.

No cases of hypercalcemia were reported during the study.

No clinically relevant findings were seen in the physical examinations or in the assessment of vital signs, height, weight, and BMI.

Conclusions:

Glucocorticoids are widely prescribed for the treatment of inflammatory and allergic disorders. However, their use is the most common cause of secondary osteoporosis. Advanced bone imaging techniques such as volumetric QCT and HR-QCT provide structural information beyond BMD as assessed by areal DXA, and growing evidence indicates that BMD only partially explains bone strength and fracture resistance. Assessing GIOP is important, especially the documentation of the glucocorticoid impact on trabecular and cortical bone and on macro- and microstructural features. Moreover, bone strength, the maximum force the bone can bear, is the most important determinant of fracture risk. It can now be assessed in vivo by a simulated mechanical test based on computerized tomography images using the method of finite element analysis.

The goal of this study was to establish the efficacy of teriparatide 20 μg/day relative to risedronate 35 mg/week in males with GIOP by the evaluation of the effects of these therapies on vBMD at the spine measured by QCT. To the best of our knowledge, this is the first study showing results of HR-QCT-based structural analysis of the vertebral trabecular bone in vivo as a tool for monitoring osteoporosis treatment in men with GIOP.

The efficacy results of the study were as follows:

- The primary objective to show that teriparatide 20 μg subcutaneously once daily is superior to risedronate 35 mg orally once weekly in the change from baseline to 18 months in lumbar spine volumetric trabecular BMD was reached with a statistically significant difference between treatments in favor of teriparatide.
- No statistically significant difference was seen between treatments in the change of lumbar spine volumetric trabecular BMD from baseline to Month 6, in the analysis of lumbar spine volumetric integral BMD at Month 6 or 18, or in the analysis of other 3-dimensional microstructural variables measured by HR-QCT at Months 6 or 18.
- The analysis of biomechanical variables evaluated by a finite element analysis in T-12 showed statistically significantly higher increases in vertebral stiffness and strength in the teriparatide arm than in the risedronate arm at Month 18, but not at Month 6.
- Between-treatment differences in mean changes in areal BMD were statistically significant at the lumbar spine and at the femoral neck, but not statistically significant at the total hip.
- Differences between treatments in the change from baseline in biochemical markers of bone turnover (P1NP and β-CTx) were statistically significant at all 3 assessed time points with the exception of β-CTx at Month 18.

The safety results of the study were as follows:

- During the study, 13 teriparatide patients (28.9%) experienced 16 SAEs compared to 22 risedronate patients (46.8%) with 42 SAEs. Most frequently reported SAEs were chronic obstructive pulmonary disease (5.43% overall) and intervertebral disc protrusion (3.26%). Three patients in the risedronate arm discontinued the study due to an SAE. Another 3 patients died due to an AE: 2 in the teriparatide arm (preferred terms: acute respiratory failure, sudden death) and 1 in the risedronate arm (chronic obstructive pulmonary disease).
- 25 patients (55.6%) in the teriparatide arm and 35 patients (74.5%) in the risedronate arm experienced at least 1 TEAE during the study. Most commonly reported TEAEs were arthralgia (7.6% of patients overall), influenza (7.6%), chronic obstructive pulmonary disease (6.5%), and peripheral edema (5.4%).
- Other safety assessments: None of the patients in the teriparatide arm compared to 5 patients in the risedronate arm (10.6%) had a new clinical fracture during the study. No cases of hypercalcemia were reported during the study. No concerns were raised in the analysis of vital signs, physical examination, height, weight, and BMI.